

E. Richter and G. Hunder

Walther Straub-Institut für Pharmakologie und Toxikologie,  
Ludwig-Maximilians-Universität München, Nussbaumstr. 26,  
D-8000 München 2, Federal Republic of Germany

NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, belongs to the group of so-called tobacco specific nitrosamines. In animals NNK has been shown to be a strong carcinogen producing mainly tumors in the lung. Although the metabolism of NNK has been extensively studied nothing is known about its fate during absorption in the small intestine, the main site of nitrosamine exposure in smokeless tobacco users and an important one even in smokers.

Using radioactive NNK,  $^{14}\text{C}$ -labelled at the carbonyl group, we investigated the first pass metabolism in jejunal segments of mice. Male NMRI mice, 25 - 30 g body weight, were either fed ad libitum or starved for 18 h. An additional group of mice was starved for 48 h and given acetone, 5 ml/kg, 24 h before the experiment. Jejunal segments of 8 - 10 cm length were perfused for 2 h at 37°C with Tyrode's solution containing  $1\ \mu\text{M}$   $^{14}\text{C}$ -NNK. Aliquots of perfusate (mucosal side) and absorbed fluid (mucosal side) were analysed for total radioactivity and for the presence of metabolites by radio-HPLC. The results are summarized in the following table. The values represent means  $\pm$  S.E. of eight segments.

| Treatment         | Percentage of metabolites in absorbate | perfusate | S/M <sup>a</sup> for total RA |
|-------------------|--|-----------|-------------------------------|
| Fed               | 58.8 $\pm$ 2.7                         | < 5       | 1.41 $\pm$ 0.05               |
| Starved           | 74.8 $\pm$ 2.2 <sup>b</sup>            | < 5       | 1.81 $\pm$ 0.08 <sup>b</sup>  |
| Starved + acetone | 76.1 $\pm$ 5.2 <sup>b</sup>            | < 5       | 1.73 $\pm$ 0.13 <sup>b</sup>  |

<sup>a</sup>Serosal to mucosal concentration ratio of total radioactivity

<sup>b</sup>Significantly different from fed animals,  $p < 0.05$

In mice fed ad libitum only 40% of the radioactive material absorbed cochromatographed with authentic NNK indicating a high first pass metabolism of NNK which was further increased by fasting but not by additional treatment with acetone. Three major metabolites could be separated, none of which cochromatographed with 4-(methylnitrosamino)-1-(3-pyridyl)butan-1-ol, the major metabolite formed in vitro by liver and lung preparations. The evaluation of the toxicological importance of the first pass metabolism of NNK has to wait for the identification of the metabolites formed by jejunal segments.

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